Complete Summary

GUIDELINE TITLE

(1) Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). (2) Interim influenza vaccination recommendations — 2004–05 influenza season. (3) Influenza antiviral medications: 2004-05 interim chemoprophylaxis and treatment guidelines.

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention (CDC). Influenza antiviral medications: 2004-05 interim chemoprophylaxis and treatment guidelines. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2004 Oct 18. 3 p.

Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2004 May 28;53(RR-6):1-40. [336 references] PubMed

Interim influenza vaccination recommendations--2004-05 influenza season. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2004 Oct 5. 2 p.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Influenza

GUIDELINE CATEGORY

Prevention
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Family Practice
Geriatrics
Infectious Diseases
Internal Medicine
Pediatrics
Pharmacology
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Emergency Medical Technicians/Paramedics
Health Care Providers
Hospitals
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

October 18, 2004 Interim Recommendations

- To provide interim recommendations on the use of antiviral medications for the 2004-05 influenza season.

October 5, 2004 Interim Recommendations

- To issue interim recommendations for influenza vaccinations during the 2004-05 season. These interim recommendations take precedence over earlier recommendations.

April 2004 Recommendations

- To guide clinical practice and policy development related to administration of the influenza vaccine and antiviral agents
- To update the 2003 recommendations issued by the Advisory Committee on Immunization Practices (ACIP) regarding the use of influenza vaccine and antiviral agents: Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2003 April 25;52 (RR-8):1-34.

TARGET POPULATION

October 18, 2004 Interim Recommendations

- People who are at high risk of serious complications from influenza

October 5, 2004 Interim Recommendations

Priority Groups for Influenza Vaccination:

- All children aged 6 to 23 months
- Adults aged 65 years and older
- Persons aged 2 to 64 years with underlying chronic medical conditions
- All women who will be pregnant during the influenza season
- Residents of nursing homes and long-term care facilities
- Children aged 6 months to 18 years on chronic aspirin therapy
- Health-care workers involved in direct patient care
- Out-of-home caregivers and household contacts of children aged

Nonpriority Groups:

- All persons not included in one of the priority groups described above.

April 2004 Recommendations

- Persons at increased risk for complications from influenza:
    - Healthy children aged 6 to 23 months and close contacts of children aged 0 to 23 months
    - Persons 65 years of age and older
    - Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions
    - Adults and children $\geq$2 years who have chronic disorders of the pulmonary or cardiovascular systems, including asthma
    - Adults and children $\geq$2 years who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV])
    - Children and adolescents (aged 6 months to 18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for developing Reye syndrome after influenza infection
    - Women who will be in the second or third trimester of pregnancy during the influenza season
- Persons who can transmit influenza to those at high risk:
    - Physicians, nurses, and other personnel in both hospital and outpatient-care settings, including medical emergency response workers (e.g., paramedics and emergency medical technicians)
    - Employees of nursing homes and chronic-care facilities who have contact with patients or residents
    - Employees of assisted living and other residences for persons in groups at high risk
    - Persons who provide home care to persons in groups at high risk
    - Household members (including children) of persons in groups at high risk
- Persons aged 50 to 64 years who wish to receive the vaccine
- Healthy persons aged 5 to 49 years who wish to receive the vaccine

INTERVENTIONS AND PRACTICES CONSIDERED

October 18, 2004 Interim Recommendations for Antiviral Medications

1. Chemoprophylaxis with amantadine or rimantadine
2. Treatment with oseltamivir or zanamivir

October 5, 2004 Interim Recommendations for Influenza Vaccination

1. Annual immunoprophylaxis with inactivated flu shot (FluZone®) for persons in priority groups.
2. Annual immunoprophylaxis with live, attenuated influenza vaccine (LAIV/FluMist®) if available, for healthy persons who are aged 5 to 49 years and are not pregnant, including health-care workers (except those who care for severely immunocompromised patients in special care units) and persons caring for children aged <6 months.
3. Patient education for persons not in one of the priority groups regarding urgent vaccine supply situation with request that they forego or defer vaccination.

April 2004 Recommendations

1. Annual immunoprophylaxis with inactivated (i.e., killed-virus) trivalent influenza vaccine (FluZone split virus, Fluvirin)

   The 2004-2005 vaccine contains the following antigens:

   - A/Fujian/411/2002(H3N2)-like (manufacturers may use the antigenically equivalent A/Wyoming/3/2003[H3N2] virus)
   - A/New Caledonia/20/99 (H1N1)-like
   - B/Shanghai/361/2002-like strains (manufacturers may use the antigenically equivalent B/Jilin/20/2003 virus or B/Jiangsu/10/2003 virus
2. Annual immunoprophylaxis with live, attenuated influenza vaccine (FluMist)
3. Influenza-specific antiviral drugs (amantadine, rimantadine, zanamivir, oseltamivir) for chemoprophylaxis or therapy of influenza A infection

MAJOR OUTCOMES CONSIDERED

- Influenza-related morbidity and mortality rates
- Influenza-related hospitalization rates
- Cost effectiveness of influenza vaccination
- Side effects and adverse reactions of influenza vaccination and antiviral agents

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Influenza vaccination can reduce both health-care costs and productivity losses associated with influenza illness. Economic studies of influenza vaccination of persons aged $\geq$65 years conducted in the United States have reported overall societal cost-savings and substantial reductions in hospitalization and death. Studies of adults aged <65 years have shown that vaccination can reduce both direct medical costs and indirect costs from work absenteeism. Reductions of 34 to 44% in physician visits, 32 to 45% in lost workdays, and 25% in antibiotic use for influenza-associated illness have been reported. One cost-effectiveness analysis estimated a cost of approximately $60 to $4,000/illness averted among healthy persons aged 18 to 64 years, depending on the cost of vaccination, the influenza attack rate, and vaccine effectiveness against influenza-like illness. Another cost-benefit economic model estimated an average annual savings of

$13.66/person vaccinated. In the second study, 78% of all costs prevented were costs from lost work productivity, whereas the first study did not include productivity losses from influenza illness. Economic studies specifically evaluating the cost-effectiveness of vaccinating persons aged 50 to 64 years are not available, and the number of studies that examine the economics of routinely vaccinating children is limited. However, in a study that included all age groups, cost utility improved with increasing age and among those with chronic medical conditions. Among persons aged ≥65 years, vaccination resulted in a net savings per quality-adjusted-life-year (QALY) gained and resulted in costs of $23 to $256/quality-adjusted-life-year among younger age groups. Additional studies of the relative cost-effectiveness and cost utility of influenza vaccination among children and among adults aged <65 years are needed and should be designed to account for year-to-year variations in influenza attack rates, illness severity, and vaccine efficacy when evaluating the long-term costs and benefits of annual vaccination.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Notice from the National Guideline Clearinghouse (NGC) and the Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices (CDC, ACIP): On October 5, 2004, The Centers for Disease Control and Preventions (CDC) was notified by Chiron Corporation that none of its influenza vaccine (Fluvirin®) would be available for distribution in the United States for the 2004–05 influenza season. The company indicated that the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom, where Chiron´s Fluvirin vaccine is produced, has suspended the company´s license to manufacture Fluvirin vaccine in its Liverpool facility for 3 months, preventing any release of this vaccine for this influenza season. This action will reduce by approximately one half the expected supply of trivalent inactivated vaccine (flu shot) available in the United States for the 2004–05 influenza season.

The remaining supply of influenza vaccine expected to be available in the United States this season is nearly 54 million doses of Fluzone® (inactivated flu shot) manufactured by Aventis Pasteur, Inc. Of these doses, approximately 30 million doses already have been distributed by the manufacturer. In addition, approximately 1.1 million doses of live attenuated influenza vaccine (LAIV/FluMist®) manufactured by MedImmune will be available this season.

Because of this urgent situation, CDC, in coordination with its Advisory Committee for Immunization Practices (ACIP), issued interim recommendations for influenza

vaccination during the 2004–05 season. These interim recommendations were formally recommended by ACIP on October 5, 2004, and take precedence over earlier recommendations.

Subsequently, on October 18, 2004, the CDC issued interim recommendations for the use of Influenza Antiviral Medications. These are described below in the section titled "Recommendations for the Use of Antiviral Agents for Influenza."

The interim recommendations for the use of the influenza vaccine and antiviral medications are available on the CDC Web site.

October 5, 2004 Interim Recommendations for Influenza Vaccination

Priority Groups for Influenza Vaccination

The following priority groups for vaccination with inactivated influenza vaccine this season are considered to be of equal importance and are:

- All children aged 6 to 23 months
- Adults aged 65 years and older
- Persons aged 2 to 64 years with underlying chronic medical conditions
- All women who will be pregnant during the influenza season
- Residents of nursing homes and long-term care facilities
- Children aged 6 months to 18 years on chronic aspirin therapy
- Health-care workers involved in direct patient care
- Out-of-home caregivers and household contacts of children aged <6 months.

Other Vaccination Recommendations

- Persons in priority groups identified above should be encouraged to search locally for vaccine if their regular health-care provider does not have vaccine available.
- Intranasally administered, live, attenuated influenza vaccine, if available, should be encouraged for healthy persons who are aged 5 to 49 years and are not pregnant, including health-care workers (except those who care for severely immunocompromised patients in special care units) and persons caring for children aged <6 months.
- Certain children aged <9 years require 2 doses of vaccine if they have not previously been vaccinated. All children at high risk for complications from influenza, including those aged 6 to 23 months, who present for vaccination, should be vaccinated with a first or second dose, depending on vaccination status. However, doses should not be held in reserve to ensure that 2 doses will be available. Instead, available vaccine should be used to vaccinate persons in priority groups on a first-come, first-serve basis.

Vaccination of Persons in Nonpriority Groups

Persons who are not included in one of the priority groups described above should be informed about the urgent vaccine supply situation and asked to forego or defer vaccination.

Persons Who Should Not Receive Influenza Vaccine

Persons in the following groups should not receive influenza vaccine before talking with their doctor:

- persons with a severe allergy (i.e., anaphylactic allergic reaction) to hens' eggs and
- persons who previously had onset of Guillain-Barré syndrome during the 6 weeks after receiving influenza vaccine.

April 2004 Recommendations for Influenza Vaccination

Primary Changes and Updates in the Recommendations

The 2004 recommendations include four principal changes or updates:

1. The Advisory Committee on Immunization Practices (ACIP) recommends that healthy children aged 6 to 23 months, and close contacts of children aged 0 to 23 months, be vaccinated against influenza (see Target Groups for Vaccination below).
2. Inactivated vaccine is preferred over live, attenuated influenza vaccine (LAIV) for vaccinating household members, health-care workers, and others who have close contact with severely immunosuppressed persons during periods when such persons require care in a protected environment. If a health-care worker receives LAIV, the health-care worker should refrain from contact with severely immunosuppressed patients for 7 days after vaccine receipt. No preference exists for inactivated vaccine use by health-care workers or other persons who have close contact with persons with lesser degrees of immunosuppression (see Live Attenuated Influenza Vaccine Recommendations/Close Contacts of Persons at High Risk for Complications from Influenza below).
3. Severely immunosuppressed persons should not administer LAIV. However, other persons at high risk for influenza complications may administer LAIV (see Personnel Who May Administer LAIV below).
4. The 2004–2005 trivalent vaccine virus strains are A/Fujian/411/2002 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Shanghai/361/2002-like antigens. For the A/Fujian/411/2002 (H3N2)-like antigen, manufacturers may use the antigenically equivalent A/Wyoming/3/2003 [H3N2] virus, and for the B/Shanghai/361/2002-like antigen, manufacturers may use the antigenically equivalent B/Jilin/20/2003 virus or B/Jiangsu/10/2003 virus (see Influenza Vaccine Composition in the original guideline document).
5. The Centers for Disease Control and Prevention (CDC) and other agencies will assess the vaccine supply throughout the manufacturing period and will make recommendations in the summer preceding the 2004–2005 influenza season regarding the need for tiered timing of vaccination of different risk groups.

Recommendations for Using Inactivated and Live, Attenuated Influenza Vaccine

Both the inactivated influenza vaccine and LAIV can be used to reduce the risk of influenza. LAIV is only approved for use among healthy persons aged 5 to 49 years. Inactivated influenza vaccine is approved for persons aged $\geq$6 months,

including those with high-risk conditions (see following sections on inactivated influenza vaccine and live, attenuated influenza vaccine).

Target Groups for Vaccination

Persons at Increased Risk for Complications

Vaccination is recommended for the following groups of persons who are at increased risk for complications from influenza:

- persons aged ≥65 years
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV])
- children and adolescents (aged 6 months to 18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for developing Reye syndrome after influenza infection
- women who will be pregnant during the influenza season
- children aged 6 to 23 months

Persons Aged 50 to 64 Years

Vaccination is recommended for persons aged 50 to 64 years because this group has an increased prevalence of persons with high-risk conditions.

Persons Who Can Transmit Influenza to Those at High Risk

Persons who are clinically or subclinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce influenza-related deaths among persons at high risk. Evidence from two studies indicates that vaccination of health-care personnel is associated with decreased deaths among nursing home patients. Health-care workers should be vaccinated against influenza annually. Facilities that employ heath-care workers are strongly encouraged to provide vaccine to workers by using approaches that maximize immunization rates. This will protect health-care workers, their patients, and communities, and will improve prevention and patient safety and reduce disease burden. Health-care workers' influenza immunization rates should be regularly measured and reported. Although rates of health-care worker vaccination are typically <40%, with moderate effort, organized campaigns can attain higher rates of vaccination among this population. The following groups should be vaccinated:

- physicians, nurses, and other personnel in both hospital and outpatient-care settings, including medical emergency response workers (e.g., paramedics and emergency medical technicians)
- employees of nursing homes and chronic-care facilities who have contact with patients or residents
- employees of assisted living and other residences for persons in groups at high risk
- persons who provide home care to persons in groups at high risk
- household contacts (including children) of persons in groups at high risk

In addition, because children aged 0 to 23 months are at increased risk for influenza-related hospitalization, vaccination is encouraged for their household contacts and out-of-home caregivers, particularly for contacts of children aged 0 to 5 months because influenza vaccines have not been approved by the U.S. Food and Drug Administration (FDA) for use among children aged <6 months.

Healthy persons aged 5 to 49 years in these groups who are not contacts of severely immunosuppressed persons (see Live, Attenuated Influenza Vaccine Recommendations) can receive either LAIV or inactivated influenza vaccine. All other persons in this group should receive inactivated influenza vaccine.

Additional Information Regarding Vaccination of Specific Populations

Pregnant Women

Because of the increased risk for influenza-related complications, women who will be pregnant during the influenza season should be vaccinated. Vaccination can occur in any trimester. One study of influenza vaccination of >2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine.

Healthy Young Children

Because children aged 6 to 23 months are at substantially increased risk for influenza-related hospitalizations, ACIP recommends vaccination of all children in this age group. ACIP continues to recommend influenza vaccination of persons aged $\geq$6 months who have high-risk medical conditions.

The current inactivated influenza vaccine is not approved by the U.S. Food and Drug Administration (FDA) for use among children aged <6 months, the pediatric group at greatest risk for influenza-related complications. Vaccinating their household contacts and out-of-home caregivers might decrease the probability of influenza infection among these children.

Beginning in March 2003, the group of children eligible for influenza vaccine coverage under the Vaccines for Children (VFC) program was expanded to include all VFC-eligible children aged 6 to 23 months and VFC-eligible children aged 2 to 18 years who are household contacts of children aged 0 to 23 months.

Persons Infected with HIV

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with human immunodeficiency virus (HIV) infection. However, a retrospective study of young and middle-aged women enrolled in Tennessee's Medicaid program determined that the attributable risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than during the peri-influenza periods. The risk for hospitalization was higher for HIV-infected women than for women with other well-recognized high-risk conditions, including chronic heart and lung diseases. Another study estimated that the risk for influenza-related death was 9.4 to 14.6/10,000 persons with acquired immune deficiency syndrome (AIDS) compared with 0.09 to 0.10/10,000 among all persons aged 25 to 54 years and 6.4 to 7.0/10,000 among persons aged $\geq$65 years. Other reports demonstrate that influenza symptoms might be prolonged and the risk for complications from influenza increased for certain HIV-infected persons.

Influenza vaccination has been demonstrated to produce substantial antibody titers against influenza among vaccinated HIV-infected persons who have minimal AIDS-related symptoms and high CD4+ T-lymphocyte cell counts. A limited, randomized, placebo-controlled trial determined that influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected persons with a mean of 400 CD4+ T-lymphocyte cells/mm^3; a limited number of persons with CD4+ T-lymphocyte cell counts of <200 were included in that study. A nonrandomized study among HIV-infected persons determined that influenza vaccination was most effective among persons with >100 $CD4^+$ cells and among those with <30,000 viral copies of HIV type 1/mL. Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers; a second dose of vaccine does not improve the immune response in these persons.

One study reported that HIV ribonucleic acid (RNA) levels increased transiently in one HIV-infected patient after influenza infection. Studies have demonstrated a transient (i.e., 2 to 4 week) increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration. Other studies using similar laboratory techniques have not documented a substantial increase in the replication of HIV. Deterioration of CD4+ T-lymphocyte cell counts or progression of HIV disease has not been demonstrated among HIV-infected persons after influenza vaccination compared with unvaccinated persons. Limited information is available concerning the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza infection or influenza vaccination. Because influenza can result in serious illness and because influenza vaccination can result in the production of protective antibody titers, vaccination will benefit many HIV-infected patients, including HIV-infected pregnant women.

Breastfeeding Mothers

Influenza vaccine does not affect the safety of mothers who are breastfeeding or their infants. Breastfeeding does not adversely affect the immune response and is not a contraindication for vaccination.

Travelers

The risk for exposure to influenza during travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year. In the temperate regions of the Southern Hemisphere, the majority of influenza activity occurs during April through September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large organized tourist groups (e.g., on cruise ships) that include persons from areas of the world where influenza viruses are circulating. Persons at high risk for complications of influenza who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to:

- travel to the tropics
- travel with large organized tourist groups at any time of year
- travel to the Southern Hemisphere during April through September

No information is available regarding the benefits of revaccinating persons before summer travel who were already vaccinated in the preceding fall. Persons at high risk who received the previous season's vaccine before travel should be revaccinated with the current vaccine in the following fall or winter. Persons aged $\geq$50 years and others at high risk might wish to consult with their physicians before embarking on travel during the summer to discuss the symptoms and risks for influenza and the advisability of carrying antiviral medications for either prophylaxis or treatment of influenza.

General Population

In addition to the groups for which annual influenza vaccination is recommended, physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza (the vaccine can be administered to children $\geq$6 months), depending on vaccine availability (see the section titled "Influenza Vaccine Supply" in the original guideline document). Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories) should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics.

Comparison of LAIV with Inactivated Influenza Vaccine

Both inactivated influenza vaccine and LAIV are available to reduce the risk of influenza infection and illness. However, the vaccines also differ in key ways (see Table 3 in the original guideline document).

Major Similarities

LAIV and inactivated influenza vaccine contain strains of influenza viruses that are antigenically equivalent to the annually recommended strains: one influenza A (H3N2) virus, one A (H1N1) virus, and one B virus. Each year, one or more virus strains might be changed on the basis of global surveillance for influenza viruses and the emergence and spread of new strains. Viruses for both vaccines are grown in eggs. Both vaccines are administered annually to provide optimal

protection against influenza infection (see Table 3 in the original guideline document).

Major Differences

Inactivated influenza vaccine contains killed viruses, whereas LAIV contains attenuated viruses still capable of replication. LAIV is administered intranasally by sprayer, whereas inactivated influenza vaccine is administered intramuscularly by injection. LAIV is more expensive than inactivated influenza vaccine. LAIV is approved for use only among healthy persons aged 5 to 49 years; inactivated influenza vaccine is approved for use among persons aged $\geq$6 months, including those who are healthy and those with chronic medical conditions (see Table 3 in the original guideline document).

Inactivated Influenza Vaccine Recommendations

Persons Who Should Not Be Vaccinated with Inactivated Influenza Vaccine

Inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine without first consulting a physician (see the section of the National Guideline Clearinghouse complete summary entitled "Benefits/Harms of Implementing the Guideline Recommendations"). Prophylactic use of the antiviral agents is an option for preventing influenza among such persons. However, persons who have a history of anaphylactic hypersensitivity to vaccine components but who are also at high risk for complications from influenza can benefit from vaccine after appropriate allergy evaluation and desensitization. Information regarding vaccine components can be found in package inserts from each manufacturer. Persons with acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate the use of influenza vaccine, particularly among children with mild upper respiratory tract infection or allergic rhinitis.

Dosage

Dosage recommendations vary according to age group (see Table 4 in the original guideline document). Among previously unvaccinated children aged <9 years, 2 doses administered $\geq$1 month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. If a child aged <9 years receiving vaccine for the first time does not receive a second dose of vaccine within the same season, only 1 dose of vaccine should be administered the following season. Two doses are not required at that time. Among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season. Even when the current influenza vaccine contains one or more antigens administered in previous years, annual vaccination with the current vaccine is necessary because immunity declines during the year after vaccination. Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.

Route

The intramuscular route is recommended for influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle. A needle length ≥1 inch can be considered for these age groups because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children.

Infants and young children should be vaccinated in the anterolateral aspect of the thigh. ACIP recommends a needle length of 7/8 to 1 inch for children aged <12 months for intramuscular vaccination into the anterolateral thigh. When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of 7/8 to 1 1/4 inches is recommended.

Side Effects and Adverse Reactions

When educating patients about potential side effects, clinicians should emphasize that (1) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and (2) coincidental respiratory disease unrelated to influenza vaccination can occur after vaccination. See the National Guideline Clearinghouse Guideline Summary field titled "Benefits/Harms of Implementing the Guideline Recommendations" for more information.

Live, Attenuated Influenza Vaccine Recommendations

Using Live, Attenuated Influenza Vaccine

LAIV is an option for vaccination of healthy persons aged 5 to 49 years, including persons in close contact with groups at high risk and those wanting to avoid influenza. Possible advantages of LAIV include its potential to induce a broad mucosal and systemic immune response, its ease of administration, and the acceptability of an intranasal rather than intramuscular route of administration.

Persons Who Should Not Be Vaccinated with LAIV

The following populations should not be vaccinated with LAIV:

- persons aged <5 years or those aged ≥50 years*
- persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including such metabolic diseases as diabetes, renal dysfunction, and hemoglobinopathies; or persons with known or suspected immunodeficiency diseases or who are receiving immunosuppressive therapies*
- children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza infection)*
- persons with a history of Guillain-Barre Syndrome (GBS)
- pregnant women*
- persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs

* These persons should receive inactivated influenza vaccine.

Close Contacts of Persons at High Risk for Complications from Influenza

Close contacts of persons at high risk for complications from influenza should receive influenza vaccine to reduce transmission of wild-type influenza viruses to persons at high risk. Use of inactivated influenza vaccine is preferred for vaccinating household members, health-care workers, and others who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) during those periods in which the immunosuppressed person requires care in a protective environment. The rationale for not using LAIV among health-care workers caring for such patients is the theoretical risk that a live, attenuated vaccine virus could be transmitted to the severely immunosuppressed person and cause disease. No preference exists for inactivated influenza vaccine use by health-care workers or other persons who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with diabetes, persons with asthma taking corticosteroids, or persons infected with human immunodeficiency virus), and no preference exists for inactivated influenza vaccine use by health-care workers or other healthy persons aged 5 to 49 years in close contact with all other groups at high risk.

If a health-care worker receives LAIV, that worker should refrain from contact with severely immunosuppressed patients as described previously for 7 days after vaccine receipt. Hospital visitors who have received LAIV should refrain from contact with severely immunosuppressed persons for 7 days after vaccination; however, such persons need not be excluded from visitation of patients who are not severely immunosuppressed.

Personnel Who May Administer LAIV

Low-level introduction of vaccine viruses into the environment is likely unavoidable when administering LAIV. The risk of acquiring vaccine viruses from the environment is unknown but likely to be limited. Severely immunosuppressed persons should not administer LAIV. However, other persons at high risk for influenza complications may administer LAIV. These include persons with underlying medical conditions placing them at high risk or who are likely to be at risk, including pregnant women, persons with asthma, and persons aged $\geq$50 years.

LAIV Dosage and Administration

LAIV is intended for intranasal administration only and should not be administered by the intramuscular, intradermal, or intravenous route. LAIV must be stored at minus 15 degrees C or colder. LAIV should not be stored in a frost-free freezer (because the temperature might cycle above minus 15 degrees C), unless a manufacturer-supplied freezer box is used. LAIV must be thawed before administration. This can be accomplished by holding an individual sprayer in the palm of the hand until thawed, with subsequent immediate administration. Alternatively, the vaccine can be thawed in a refrigerator and stored at 2 degrees C to 8 degrees C for $\leq$24 hours before use. Vaccine should not be refrozen after thawing. LAIV is supplied in a prefilled single-use sprayer containing 0.5 mL of vaccine. Approximately 0.25 mL (i.e., half of the total sprayer contents) is sprayed into the first nostril while the recipient is in the upright position. An attached dose-divider clip is removed from the sprayer to administer the second half of the dose into the other nostril. If the vaccine recipient sneezes after administration, the dose should not be repeated.

LAIV should be administered annually according to the following schedule:

- Children aged 5 to 8 years previously unvaccinated at any time with either LAIV or inactivated influenza vaccine should receive 2 doses (one dose equals 0.5 mL, divided equally between each nostril) of LAIV separated by 6 to 10 weeks.
- Children aged 5 to 8 years previously vaccinated at any time with either LAIV or inactivated influenza vaccine should receive 1 dose of LAIV. They do not require a second dose.
- Persons aged 9 to 49 years should receive 1 dose of LAIV.
- LAIV can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infection with or without fever). However, if clinical judgment indicates nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness.
- Whether concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine is unknown. In the absence of specific data indicating interference, following the ACIP general recommendations for immunization is prudent. Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. An inactivated vaccine can be administered either simultaneously or at any time before or after LAIV. Two live vaccines not administered on the same day should be administered $\geq$4 weeks apart when possible.

LAIV and Use of Influenza Antiviral Medications

The effect on safety and efficacy of LAIV coadministration with influenza antiviral medications has not been studied. However, because influenza antivirals reduce replication of influenza viruses, LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy, and influenza antiviral medications should not be administered for 2 weeks after receipt of LAIV.

LAIV Storage

LAIV must be stored at minus 15 degrees C or colder. LAIV should not be stored in a frost-free freezer because the temperature might cycle above minus 15 degrees C, unless a manufacturer-supplied freezer box or other strategy is used. LAIV can be thawed in a refrigerator and stored at 2 degrees C to 8 degrees C for $\leq$24 hours before use. It should not be refrozen after thawing. Additional information is available at Wyeth Product Quality (1-800-411-0086) or at http://www.flumist.com/.

Side Effects and Adverse Reactions

See the National Guideline Clearinghouse Guideline Summary field titled "Benefits/Harms of Implementing the Guideline Recommendations."

Recommended Vaccines for Different Age Groups

When vaccinating children aged 6 months to 3 years, health-care providers should use inactivated influenza vaccine that has been approved by FDA for this age group. Inactivated influenza vaccine from Aventis Pasteur, Inc., (FluZone split-virus) is approved for use among persons aged ≥6 months. Inactivated influenza vaccine from Chiron (Fluvirin) is labeled in the United States for use only among persons aged ≥4 years because data to demonstrate efficacy among younger persons have not been provided to FDA. Live, attenuated influenza vaccine from MedImmune (FluMist) is approved for use by healthy persons aged 5 to 49 years (see Table 5 in the original guideline document).

Timing of Annual Influenza Vaccination

The annual supply of inactivated influenza vaccine and the timing of its distribution cannot be guaranteed in any year. Information regarding the supply of 2004–2005 vaccine might not be available until late summer or early fall 2004. To allow vaccine providers to plan for the upcoming vaccination season, taking into account the yearly possibility of vaccine delays or shortages and the need to ensure vaccination of persons at high risk and their contacts, ACIP recommends that vaccine campaigns conducted in October focus their efforts primarily on persons at increased risk for influenza complications and their contacts, including health-care workers. Campaigns conducted in November and later should continue to vaccinate persons at high risk and their contacts, but also vaccinate other persons who wish to decrease their risk for influenza infection. Vaccination efforts for all groups should continue into December and beyond. CDC and other public health agencies will assess the vaccine supply on a continuing basis throughout the manufacturing period and will make recommendations in the summer preceding the 2004–2005 influenza season regarding the need for tiered timing of vaccination of different risk groups.

Vaccination in October and November

The optimal time to vaccinate is usually during October through November. ACIP recommends that vaccine providers focus their vaccination efforts in October and earlier primarily on persons aged ≥50 years, persons aged <50 years at increased risk for influenza-related complications (including children aged 6 to 23 months), household contacts of persons at high risk (including out-of-home caregivers and household contacts of children aged 0 to 23 months), and health-care workers. Vaccination of children aged <9 years who are receiving vaccine for the first time should also begin in October or earlier because those persons need a booster dose 1 month after the initial dose. Efforts to vaccinate other persons who wish to decrease their risk for influenza infection should begin in November; however, if such persons request vaccination in October, vaccination should not be deferred. Materials to assist providers in prioritizing early vaccine are available at http://www.cdc.gov/flu/professionals/vaccination/index.htm (see also "Travelers" in this report).

Timing of Organized Vaccination Campaigns

Persons planning substantial organized vaccination campaigns should consider scheduling these events after mid-October because the availability of vaccine in any location cannot be ensured consistently in early fall. Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is

unavailable. Campaigns conducted before November should focus efforts on vaccination of persons aged ≥50 years, persons aged <50 years at increased risk for influenza-related complications (including children aged 6 to 23 months), health-care workers, and household contacts of persons at high-risk (including children aged 0 to 23 months) to the extent feasible.

Vaccination in December and Later

After November, many persons who should or want to receive influenza vaccine remain unvaccinated. In addition, substantial amounts of vaccine have remained unused during three of the past four influenza seasons. To improve vaccine coverage, influenza vaccine should continue to be offered in December and throughout the influenza season as long as vaccine supplies are available, even after influenza activity has been documented in the community. In the United States, seasonal influenza activity can begin to increase as early as October or November, but influenza activity has not reached peak levels in the majority of recent seasons until late December to early March (see Table 6 in the original guideline document). Therefore, although the timing of influenza activity can vary by region, vaccine administered after November is likely to be beneficial in the majority of influenza seasons. Adults develop peak antibody protection against influenza infection 2 weeks after vaccination.

Vaccination Before October

To avoid missed opportunities for vaccination of persons at high risk for serious complications, such persons should be offered vaccine beginning in September during routine health-care visits or during hospitalizations, if vaccine is available. In facilities housing older persons (e.g., nursing homes), vaccination before October typically should be avoided because antibody levels in such persons can begin to decline within a limited time after vaccination. In addition, children aged <9 years who have not been previously vaccinated and who need 2 doses before the start of the influenza season can receive their first dose in September or earlier.

Strategies for Implementing Vaccination Recommendations in Health-Care Settings

See the National Guideline Clearinghouse guideline summary field titled "Description of Implementation Strategy".

Recommendations for the Use of Antiviral Agents for Influenza

October 18, 2004 Interim Recommendations

On October 18, 2004, the CDC issued interim recommendations for the use of antiviral medications during the 2004-05 season. Local availability of these medications may vary from community to community, which could impact how these medications should be used.

1. CDC encourages the use of amantadine or rimantadine for chemoprophylaxis and use of oseltamivir or zanamivir for treatment

as supplies allow, in part to minimize the development of adamantane resistance among circulating influenza viruses.

2. People who are at high risk of serious complications from influenza may benefit most from antiviral medications. Therefore, in general, people who fall into these high risk groups should be given priority for use of influenza antiviral medications.

   Treatment

   - Any person experiencing a potentially life-threatening influenza-related illness should be treated with antiviral medications.
   - Any person at high risk for serious complications of influenza and who is within the first 2 days of illness onset should be treated with antiviral medications. (Pregnant women should consult their primary provider regarding use of influenza antiviral medications.)

   Rimantadine is not approved for treatment of children aged

   Chemoprophylaxis

   - All persons who live or work in institutions caring for people at high risk of serious complications of influenza infection should be given antiviral medications in the event of an institutional outbreak. This includes nursing homes, hospitals, and other facilities caring for persons with immunosuppressive conditions, such as HIV/AIDS. When vaccine is available, vaccinated staff require chemoprophylaxis only for the 2-week period following vaccination. Vaccinated and unvaccinated residents should receive chemoprophylaxis for the duration of institutional outbreak activity. Rapid tests or other influenza tests should be used to confirm influenza as the cause of outbreaks as soon as possible. However, treatment and chemoprophylaxis should be initiated if influenza is strongly suspected and test results are not yet available. Other outbreak control efforts such as cohorting of infected persons, and the practice of respiratory hygiene and other measures also should be implemented. For further information on detection and control of influenza outbreaks in acute care facilities, see www.cdc.gov/ncidod/hip/INFECT/flu_acute.htm.
   - All persons at high risk of serious influenza complications should be given antiviral medications if they are likely to be exposed to others infected with influenza. For example, when a high-risk person is part of a family or household in which someone else has been diagnosed with influenza, the exposed high-risk person should be given chemoprophylaxis for 7 days.

3. Antiviral medications can be considered in other situations when the available supply of such medications is locally adequate.
   - Chemoprophylaxis of persons in communities where influenza viruses are circulating, which typically lasts for 6-8 weeks:
     - Persons at high risk of serious complications who are not able to get vaccinated.
     - Persons at high risk of serious complications who have been vaccinated but have not had time to mount an immune

response to the vaccine. In adults, chemoprophylaxis should occur for a period of 2 weeks after vaccination. In children aged
    - Persons with immunosuppressive conditions who are not expected to mount an adequate antibody response to influenza vaccine.
    - Health-care workers with direct patient care responsibilities who are not able to obtain vaccine.
- Treatment of infected adults and children aged >1 year who do not have conditions placing them at high risk for serious complications secondary to influenza infection.

4. Where the supplies of both influenza vaccine and influenza antiviral medications may not be sufficient to meet demand, CDC does not recommend the use of influenza antiviral medications for chemoprophylaxis of non-high risk persons in the community.

Private Sector Sources of Influenza Antiviral Medications

Pharmaceutical distributors should be contacted directly for availability and procurement of antiviral medications.

Strategic National Stockpile (SNS)

The United States has a limited supply of influenza antiviral medications stored in the Strategic National Stockpile for emergency situations. Efforts are underway by Health and Human Services to procure additional supplies of antiviral medications. Some of the supply will be held in reserve in the event of an influenza pandemic. However, some of the supply will be made available to States and Territories for use in outbreak settings, as might occur in a hospital or long term care facility. Refer to the "Description of Implementation Strategy" field for information on requesting influenza medications from the SNS.

April 2004 Recommendations

Antiviral drugs for influenza are an adjunct to influenza vaccine for controlling and preventing influenza. However, these agents are not a substitute for vaccination. Four licensed influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir.

Amantadine and rimantadine are chemically related antiviral drugs known as adamantanes with activity against influenza A viruses but not influenza B viruses. Amantadine was approved in 1966 for chemoprophylaxis of influenza A (H2N2) infection and was later approved in 1976 for the treatment and chemoprophylaxis of influenza type A virus infections among adults and children aged $\geq$1 year. Rimantadine was approved in 1993 for treatment and chemoprophylaxis of influenza A infection among adults and prophylaxis among children. Although rimantadine is approved only for chemoprophylaxis of influenza A infection among children, certain specialists in the management of influenza consider it appropriate for treatment of influenza A among children.

Zanamivir and oseltamivir are chemically related antiviral drugs known as neuraminidase inhibitors that have activity against both influenza A and B viruses. Both zanamivir and oseltamivir were approved in 1999 for treating uncomplicated influenza infections. Zanamivir is approved for treating persons aged ≥7 years, and oseltamivir is approved for treatment for persons aged ≥1 years. In 2000, oseltamivir was approved for chemoprophylaxis of influenza among persons aged ≥13 years.

The four drugs differ in terms of their pharmacokinetics, side effects, routes of administration, approved age groups, dosages, and costs. An overview of the indications, use, administration, and known primary side effects of these medications is presented in the following sections. Information contained in this report might not represent FDA approval or approved labeling for the antiviral agents described. Package inserts should be consulted for additional information.

Role of Laboratory Diagnosis

Appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. The early diagnosis of influenza can reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. However, because certain bacterial infections can produce symptoms similar to influenza, bacterial infections should be considered and appropriately treated if suspected. In addition, bacterial infections can occur as a complication of influenza.

Influenza surveillance information as well as diagnostic testing can aid clinical judgment and help guide treatment decisions. The accuracy of clinical diagnosis of influenza based on symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza. Influenza surveillance by state and local health departments and the CDC can provide information regarding the presence of influenza viruses in the community. Surveillance can also identify the predominant circulating types, subtypes, and strains of influenza.

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, polymerase chain reaction (PCR), and immunofluorescence. Sensitivity and specificity of any test for influenza might vary by the laboratory that performs the test, the type of test used, and the type of specimen tested. Among respiratory specimens for viral isolation or rapid detection, nasopharyngeal specimens are typically more effective than throat swab specimens. As with any diagnostic test, results should be evaluated in the context of other clinical information available to health-care providers.

Commercial rapid diagnostic tests are available that can be used by laboratories in outpatient settings to detect influenza viruses within 30 minutes. These rapid tests differ in the types of influenza viruses they can detect and whether they can distinguish between influenza types. Different tests can detect (1) only influenza A viruses; (2) both influenza A and B viruses but not distinguish between the two types; or (3) both influenza A and B and distinguish between the two. The types of specimens acceptable for use (i.e., throat swab, nasal wash, or nasal swab) also vary by test. The specificity and, in particular, the sensitivity of rapid tests are lower than for viral culture and vary by test. Because of the lower sensitivity of the rapid tests, physicians should consider confirming negative tests with viral

culture or other means. Further, when interpreting results of a rapid influenza test, physicians should consider the positive and negative predictive values of the test in the context of the level of influenza activity in their community. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid diagnostic tests. Additional information regarding diagnostic testing is available at the Centers for Disease Control and Prevention (CDC) Web site.

Despite the availability of rapid diagnostic tests, collecting clinical specimens for viral culture is critical, because only culture isolates can provide specific information regarding circulating influenza subtypes and strains. This information is needed to compare current circulating influenza strains with vaccine strains, to guide decisions regarding influenza treatment and chemoprophylaxis, and to formulate vaccine for the coming year. Virus isolates also are needed to monitor the emergence of antiviral resistance and the emergence of novel influenza A subtypes that might pose a pandemic threat.

Indications for Use

Treatment

When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A illness, and zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day compared with placebo. More clinical data are available concerning the efficacy of zanamivir and oseltamivir for treatment of influenza A infection than for treatment of influenza B infection. However, in vitro data and studies of treatment among mice and ferrets, in addition to clinical studies, have documented that zanamivir and oseltamivir have activity against influenza B viruses.

Data are limited regarding the effectiveness of the four antiviral agents in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Evidence for the effectiveness of these four antiviral drugs is based principally on studies of patients with uncomplicated influenza. Data are limited and inconclusive concerning the effectiveness of amantadine, rimantadine, zanamivir, and oseltamivir for treatment of influenza among persons at high risk for serious complications of influenza. One study assessing oseltamivir treatment primarily among adults reported a reduction in complications necessitating antibiotic therapy compared with placebo. Fewer studies of the efficacy of influenza antivirals have been conducted among pediatric populations. One study of oseltamivir treatment documented a decreased incidence of otitis media among children. Inadequate data exist regarding the safety and efficacy of any of the influenza antiviral drugs for use among children aged <1 year.

To reduce the emergence of antiviral drug-resistant viruses, amantadine or rimantadine therapy for persons with influenza A illness should be discontinued as soon as clinically warranted, typically after 3 to 5 days of treatment or within 24 to 48 hours after the disappearance of signs and symptoms. The recommended duration of treatment with either zanamivir or oseltamivir is 5 days.

Chemoprophylaxis

Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in the prevention and control of influenza. Both amantadine and rimantadine are indicated for the chemoprophylaxis of influenza A infection, but not influenza B. Both drugs are approximately 70 to 90% effective in preventing illness from influenza A infection. When used as prophylaxis, these antiviral agents can prevent illness while permitting subclinical infection and the development of protective antibody against circulating influenza viruses. Therefore, certain persons who take these drugs will develop protective immune responses to circulating influenza viruses. Amantadine and rimantadine do not interfere with the antibody response to the vaccine. Both drugs have been studied extensively in nursing home populations as a component of influenza outbreak-control programs, which can limit the spread of influenza within chronic care institutions.

Among the neuraminidase inhibitor antivirals, zanamivir and oseltamivir, only oseltamivir has been approved for prophylaxis, but community studies of healthy adults indicate that both drugs are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%). Both antiviral agents have also been reported to prevent influenza illness among persons given chemoprophylaxis after a household member was diagnosed with influenza. Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited in comparison with the adamantanes. One 6-week study of oseltamivir prophylaxis among nursing home residents found a 92% reduction in influenza illness. Use of zanamivir has not been reported to impair the immunologic response to influenza vaccine. Data are not available on the efficacy of any of the four antiviral agents in preventing influenza among severely immunocompromised persons.

When determining the timing and duration for administering influenza antiviral medications for prophylaxis, factors related to cost, compliance, and potential side effects should be considered. To be maximally effective as prophylaxis, the drug must be taken each day for the duration of influenza activity in the community. However, to be most cost-effective, one study of amantadine or rimantadine prophylaxis reported that the drugs should be taken only during the period of peak influenza activity in a community.

Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun: Persons at high risk for complications of influenza still can be vaccinated after an outbreak of influenza has begun in a community. However, the development of antibodies in adults after vaccination can take approximately 2 weeks. When influenza vaccine is administered while influenza viruses are circulating, chemoprophylaxis should be considered for persons at high risk during the time from vaccination until immunity has developed. Children aged <9 years who receive influenza vaccine for the first time can require 6 weeks of prophylaxis (i.e., prophylaxis for 4 weeks after the first dose of vaccine and an additional 2 weeks of prophylaxis after the second dose).

Persons Who Provide Care to Those at High Risk: To reduce the spread of virus to persons at high risk during community or institutional outbreaks, chemoprophylaxis during peak influenza activity can be considered for

unvaccinated persons who have frequent contact with persons at high risk. Persons with frequent contact include employees of hospitals, clinics, and chronic-care facilities, household members, visiting nurses, and volunteer workers. If an outbreak is caused by a variant strain of influenza that might not be controlled by the vaccine, chemoprophylaxis should be considered for all such persons, regardless of their vaccination status.

Persons Who Have Immune Deficiencies: Chemoprophylaxis can be considered for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons infected with HIV, chiefly those with advanced HIV disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should be monitored closely if chemoprophylaxis is administered.

Other Persons: Chemoprophylaxis throughout the influenza season or during peak influenza activity might be appropriate for persons at high risk who should not be vaccinated. Chemoprophylaxis can also be offered to persons who wish to avoid influenza illness. Health-care providers and patients should make this decision on an individual basis.

Control of Influenza Outbreaks in Institutions

Using antiviral drugs for treatment and prophylaxis of influenza is a key component of influenza outbreak control in institutions. In addition to antiviral medications, other outbreak-control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, re-offering influenza vaccinations to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients. (For additional information regarding outbreak control in specific settings, refer to the additional references in the section titled "Additional Information Regarding Influenza Infection Control Among Specific Populations" in the original guideline document.)

The majority of published reports concerning use of antiviral agents to control influenza outbreaks in institutions are based on studies of influenza A outbreaks among nursing home populations where amantadine or rimantadine were used. Less information is available concerning the use of neuraminidase inhibitors in influenza A or B institutional outbreaks. When confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk, chemoprophylaxis should be started as early as possible to reduce the spread of the virus. In these situations, having preapproved orders from physicians or plans to obtain orders for antiviral medications on short notice can substantially expedite administration of antiviral medications.

When outbreaks occur in institutions, chemoprophylaxis should be administered to all residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 1 week after the end of the outbreak. The dosage for each resident should be determined individually. Chemoprophylaxis also can be offered to unvaccinated staff who provide care to persons at high risk. Prophylaxis should

be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza that is not well-matched by the vaccine.

In addition to nursing homes, chemoprophylaxis also can be considered for controlling influenza outbreaks in other closed or semiclosed settings (e.g., dormitories or other settings where persons live in close proximity). For example, chemoprophylaxis with rimantadine has been used successfully to control an influenza A outbreak aboard a large cruise ship.

To limit the potential transmission of drug-resistant virus during outbreaks in institutions, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact as much as possible between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis (see the section titled "Antiviral Drug-Resistant Strains of Influenza" in the original guideline document).

Dosage

Dosage recommendations vary by age group and medical conditions (see Table 7 in the original guideline document).

Children

Amantadine: The use of amantadine among children aged <1 year has not been adequately evaluated. The FDA-approved dosage for children aged 1 to 9 years for treatment and prophylaxis is 4.4 to 8.8 mg/kg/day, not to exceed 150 mg/day. Although further studies are needed to determine the optimal dosage for children aged 1 to 9 years, physicians should consider prescribing only 5 mg/kg/day (not to exceed 150 mg/day) to reduce the risk for toxicity. The approved dosage for children aged ≥10 years is 200 mg/day (100 mg twice a day); however, for children weighing <40 kg, prescribing 5 mg/kg/day, regardless of age, is advisable.

Rimantadine: Rimantadine is approved for prophylaxis among children aged ≥1 year and for treatment and prophylaxis among adults. Although rimantadine is approved only for prophylaxis of infection among children, certain specialists in the management of influenza consider rimantadine appropriate for treatment among children. Use of rimantadine among children aged <1 year has not been adequately evaluated. Rimantadine should be administered in one or two divided doses at a dosage of 5 mg/kg/day, not to exceed 150 mg/day for children aged 1 to 9 years. The approved dosage for children aged ≥10 years is 200 mg/day (100 mg twice a day); however, for children weighing <40 kilograms, prescribing 5 mg/kg/day, regardless of age, is recommended.

Zanamivir: Zanamivir is approved for treatment among children aged ≥7 years. The recommended dosage of zanamivir for treatment of influenza is two inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart).

Oseltamivir: Oseltamivir is approved for treatment among persons aged ≥1 year and for chemoprophylaxis among persons aged ≥13 years. Recommended treatment doses for children vary by the weight of the child: the dose recommendation for children who weigh ≤15 kg is 30 mg twice a day; for children weighing >15 to 23 kg, the dose is 45 mg twice a day; for those weighing >23 to 40 kg, the dose is 60 mg twice a day; and for children weighing >40 kg, the dose is 75 mg twice a day. The treatment dosage for persons ≥13 years is 75 mg twice daily. For children ≥13 years, the recommended dose for prophylaxis is 75 mg once a day.

Persons Aged >65 Years

Amantadine: The daily dose of amantadine for persons aged ≥65 years should not exceed 100 mg for prophylaxis or treatment, because renal function declines with increasing age. For certain elderly persons, the dose should be further reduced.

Rimantadine: Among elderly persons, the incidence and severity of central nervous system (CNS) side effects are substantially lower among those taking rimantadine at a dosage of 100 mg/day than among those taking amantadine at dosages adjusted for estimated renal clearance. However, chronically ill elderly persons have had a higher incidence of central nervous system and gastrointestinal symptoms and serum concentrations two to four times higher than among healthy, younger persons when rimantadine has been administered at a dosage of 200 mg/day.

For prophylaxis among persons aged ≥65 years, the recommended dosage is 100 mg/day. For treatment of older persons in the community, a reduction in dosage to 100 mg/day should be considered if they experience side effects when taking a dosage of 200 mg/day. For treatment of older nursing home residents, the dosage of rimantadine should be reduced to 100 mg/day.

Zanamivir and Oseltamivir: No reduction in dosage is recommended on the basis of age alone.

Persons with Impaired Renal Function

Amantadine: A reduction in dosage is recommended for patients with creatinine clearance ≤50 mL/min/1.73m^2. Guidelines for amantadine dosage based on creatinine clearance are found in the package insert. Because recommended dosages on the basis of creatinine clearance might provide only an approximation of the optimal dose for a given patient, such persons should be observed carefully for adverse reactions. If necessary, further reduction in the dose or discontinuation of the drug might be indicated because of side effects. Hemodialysis contributes minimally to amantadine clearance.

Rimantadine: A reduction in dosage to 100 mg/day is recommended for persons with creatinine clearance <10 mL/min. Because of the potential for accumulation of rimantadine and its metabolites, patients with any degree of renal insufficiency, including elderly persons, should be monitored for adverse effects, and either the dosage should be reduced or the drug should be discontinued, if necessary. Hemodialysis contributes minimally to drug clearance.

Zanamivir: Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Among patients with renal failure who were administered a single intravenous dose of zanamivir, decreases in renal clearance, increases in half-life, and increased systemic exposure to zanamivir were observed. However, a small number of healthy volunteers who were administered high doses of intravenous zanamivir tolerated systemic levels of zanamivir that were substantially higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose. On the basis of these considerations, the manufacturer recommends no dose adjustment for inhaled zanamivir for a 5-day course of treatment for patients with either mild-to-moderate or severe impairment in renal function.

Oseltamivir: Serum concentrations of oseltamivir carboxylate (GS4071), the active metabolite of oseltamivir, increase with declining renal function. For patients with creatinine clearance of 10 to 30 mL/min, a reduction of the treatment dosage of oseltamivir to 75 mg once daily and in the prophylaxis dosage to 75 mg every other day is recommended. No treatment or prophylaxis dosing recommendations are available for patients undergoing routine renal dialysis treatment.

Persons with Liver Disease

Amantadine: No increase in adverse reactions to amantadine has been observed among persons with liver disease. Rare instances of reversible elevation of liver enzymes among patients receiving amantadine have been reported, although a specific relationship between the drug and such changes has not been established.

Rimantadine: A reduction in dosage to 100 mg/day is recommended for persons with severe hepatic dysfunction.

Zanamivir and Oseltamivir: Neither of these medications has been studied among persons with hepatic dysfunction.

Persons with Seizure Disorders

Amantadine: An increased incidence of seizures has been reported among patients with a history of seizure disorders who have received amantadine. Patients with seizure disorders should be observed closely for possible increased seizure activity when taking amantadine.

Rimantadine: Seizures (or seizure-like activity) have been reported among persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine. The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been adequately evaluated.

Zanamivir and Oseltamivir: Seizure events have been reported during postmarketing use of zanamivir and oseltamivir, although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

Route

Amantadine, rimantadine, and oseltamivir are administered orally. Amantadine and rimantadine are available in tablet or syrup form, and oseltamivir is available in capsule or oral suspension form. Zanamivir is available as a dry powder that is self-administered via oral inhalation by using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of correct use of this device.

Side Effects and Adverse Reactions

See the National Guideline Clearinghouse Guideline Summary field titled "Benefits/Harms of Implementing the Guideline Recommendations."

Use During Pregnancy

No clinical studies have been conducted regarding the safety or efficacy of amantadine, rimantadine, zanamivir, or oseltamivir for pregnant women; only two cases of amantadine use for severe influenza illness during the third trimester have been reported. However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at substantially high doses. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus (see manufacturers' package inserts).

Drug Interactions

Careful observation is advised when amantadine is administered concurrently with drugs that affect the central nervous system (CNS), including central nervous system stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase the incidence of adverse central nervous system reactions. No clinically significant interactions between rimantadine and other drugs have been identified.

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically important drug interactions have been predicted on the basis of in vitro data and data from studies involving rats.

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway, a potential exists for interaction with other agents excreted by this pathway. For example, coadministration of oseltamivir and probenecid resulted in reduced clearance of oseltamivir carboxylate by approximately 50% and a corresponding approximate twofold increase in the plasma levels of oseltamivir carboxylate.

No published data are available concerning the safety or efficacy of using combinations of any of these four influenza antiviral drugs. For more detailed

information concerning potential drug interactions for any of these influenza antiviral drugs, the package inserts should be consulted.

Antiviral Drug-Resistant Strains of Influenza

Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa. Drug-resistant viruses can appear in approximately one third of patients when either amantadine or rimantadine is used for therapy. During the course of amantadine or rimantadine therapy, resistant influenza strains can replace sensitive strains within 2 to 3 days of starting therapy. Resistant viruses have been isolated from persons who live at home or in an institution where other residents are taking or have recently taken amantadine or rimantadine as therapy; however, the frequency with which resistant viruses are transmitted and their impact on efforts to control influenza are unknown. Amantadine- and rimantadine-resistant viruses are not more virulent or transmissible than sensitive viruses. The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses.

Persons who have influenza A infection and who are treated with either amantadine or rimantadine can shed sensitive viruses early in the course of treatment and later shed drug-resistant viruses, especially after 5 to 7 days of therapy. Such persons can benefit from therapy even when resistant viruses emerge.

Resistance to zanamivir and oseltamivir can be induced in influenza A and B viruses in vitro, but induction of resistance requires multiple passages in cell culture. By contrast, resistance to amantadine and rimantadine in vitro can be induced with fewer passages in cell culture. Development of viral resistance to zanamivir and oseltamivir during treatment has been identified but does not appear to be frequent. In clinical treatment studies using oseltamivir, 1.3% of posttreatment isolates from patients aged $\geq$13 years and 8.6% among patients aged 1 to 12 years had decreased susceptibility to oseltamivir. No isolates with reduced susceptibility to zanamivir have been reported from clinical trials, although the number of posttreatment isolates tested is limited, and the risk for emergence of zanamivir-resistant isolates cannot be quantified. Only one clinical isolate with reduced susceptibility to zanamivir, obtained from an immunocompromised child on prolonged therapy, has been reported. Available diagnostic tests are not optimal for detecting clinical resistance to the neuraminidase inhibitor antiviral drugs, and additional tests are being developed. Postmarketing surveillance for neuraminidase inhibitor-resistant influenza viruses is being conducted.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Efficacy and Effectiveness of Inactivated Vaccine

The effectiveness of inactivated influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. The majority of vaccinated children and young adults develop high postvaccination hemagglutination inhibition antibody titers. These antibody titers are protective against illness caused by strains similar to those in the vaccine.

- Adults aged <65 years: When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents influenza illness in approximately 70 to 90% of healthy adults aged <65 years. Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including use of antibiotics, when the vaccine and circulating viruses are well-matched.
- Children: Children aged as young as 6 months can develop protective levels of antibody after influenza vaccination, although the antibody response among children at high risk of influenza-related complications might be lower than among healthy children. Other studies report that trivalent inactivated influenza vaccine decreases the incidence of influenza-associated otitis media among young children by approximately 30%.
- Adults aged >65 years: Older persons and persons with certain chronic diseases might develop lower postvaccination antibody titers than healthy young adults and thus can remain susceptible to influenza-related upper respiratory tract infection. The vaccine can be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults $\geq$65 years with and without high-risk medical conditions (e.g., heart disease and diabetes). Among elderly persons living outside of nursing homes or similar chronic-care facilities, influenza vaccine is 30 to 70% effective in preventing hospitalization for pneumonia and influenza. Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and deaths. Among this population, the vaccine can be 50 to 60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death, although the effectiveness in preventing influenza illness often ranges from 30 to 40%.

Efficacy and Effectiveness of Live Attenuated Influenza Virus (LAIV)

- Healthy Children. A randomized, double-blind, placebo-controlled trial among 1,602 healthy children initially aged 15 to 71 months assessed the efficacy of trivalent LAIV against culture-confirmed influenza during two seasons. This trial included subsets of 238 healthy children (163 vaccinees and 75 placebo recipients) aged 60 to 71 months who received 2 doses and 74 children (54

vaccinees and 20 placebo recipients) aged 60 to 71 months who received a single dose during season one, and a subset of 544 children (375 vaccinees and 169 placebo recipients) aged 60 to 84 months during season two. Children who continued from season one to season two remained in the same study group. In season one, when vaccine and circulating virus strains were well-matched, efficacy was 93% for all participants, regardless of age, among persons receiving 2 doses of LAIV. Efficacy was 87% in the 60 to 71-month subset for those who received 2 doses, and was 91% in the subset for those who received 1 or 2 doses. In season two, when the A (H3N2) component was not well-matched between vaccine and circulating virus strains, efficacy was 86% overall and 87% among those aged 60 to 84 months. The vaccine was 92% efficacious in preventing culture-confirmed influenza during the two-season study. Other results included a 27% reduction in febrile otitis media and a 28% reduction in otitis media with concomitant antibiotic use. Receipt of LAIV also resulted in decreased fever and otitis media among vaccine recipients who experienced influenza.

- Healthy Adults. A randomized, double-blind, placebo-controlled trial among 4,561 healthy working adults aged 18 to 64 years assessed multiple endpoints, including reductions in illness, absenteeism, health-care visits, and medication use during peak and total influenza outbreak periods). The study was conducted during the 1997 to 1998 influenza season, when the vaccine and circulating A (H3N2) strains were not well-matched. The study did not include testing of viruses by a laboratory. During peak outbreak periods, no difference was identified between LAIV and placebo recipients experiencing any febrile episodes. However, vaccination was associated with reductions in severe febrile illnesses of 19% and febrile upper respiratory tract illnesses of 24%. Vaccination also was associated with fewer days of illness, fewer days of work lost, fewer days with health-care provider visits, and reduced use of prescription antibiotics and over-the-counter medications.

  Among the subset of 3,637 healthy adults aged 18 to 49 years, LAIV recipients (n = 2,411) had 26% fewer febrile upper-respiratory illness episodes; 27% fewer lost work days as a result of febrile upper respiratory illness; and 18% to 37% fewer days of health-care provider visits caused by febrile illness, compared with placebo recipients (n = 1,226). Days of antibiotic use were reduced by 41 to 45% in this age subset.

  Another randomized, double-blind, placebo-controlled challenge study among 92 healthy adults (LAIV, n = 29; placebo, n = 31; inactivated influenza vaccine, n = 32) aged 18 to 41 years assessed the efficacy of both LAIV and inactivated vaccine. The overall efficacy of LAIV and inactivated influenza vaccine in preventing laboratory-documented influenza from all three influenza strains combined was 85% and 71%, respectively, on the basis of experimental challenge by viruses to which study participants were susceptible before vaccination. The difference between the two vaccines was not statistically significant.

Antiviral Agents Used as Treatment

October 18, 2004 Interim Recommendations for the Use of Antiviral Medications

Use of the interim recommendations may reduce the impact of influenza on persons at high risk for developing severe complications secondary to infection.

April 2004 Recommendations

When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A illness, and zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day, compared with placebo.

Chemoprophylaxis with Antiviral Agents

- Both amantadine and rimantadine are indicated for chemoprophylaxis of influenza A infection, but not influenza B. Both drugs are approximately 70 to 90% effective in preventing illness from influenza A infection. When used as prophylaxis, these antiviral agents can prevent illness while permitting subclinical infection and the development of protective antibody against circulating influenza viruses. Therefore, certain persons who take these drugs will develop protective immune responses to circulating influenza viruses. Amantadine and rimantadine do not interfere with the antibody response to the vaccine. Both drugs have been studied extensively among nursing home populations as a component of influenza outbreak control programs, which can limit the spread of influenza within chronic care institutions.
- Among the neuraminidase inhibitor antivirals, zanamivir and oseltamivir, only oseltamivir has been approved for prophylaxis, but community studies of healthy adults indicate that both drugs are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%). Both antiviral agents have also been reported to prevent influenza illness among persons administered chemoprophylaxis after a household member was diagnosed with influenza. Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited in comparison with the adamantanes. One 6-week study of oseltamivir prophylaxis among nursing home residents reported a 92% reduction in influenza illness. Use of zanamivir has not been reported to impair the immunologic response to influenza vaccine. Data are not available regarding the efficacy of any of the four antiviral agents in preventing influenza among severely immunocompromised persons.

POTENTIAL HARMS

Inactivated Vaccine

Local Reactions

In placebo-controlled studies among adults, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10 to 64% of patients) that lasts <2 days. These local reactions typically are mild and rarely interfere with the person's ability to conduct usual daily activities.

Systemic Reactions

- Fever, malaise, myalgia, and other systemic symptoms can occur after vaccination and most often affect persons who have had no prior exposure to the influenza virus antigens in the vaccine (e.g., young children). These reactions begin 6 to 12 hours after vaccination and can persist for 1 to 2 days.
- Recent placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of split-virus influenza vaccine is not associated with higher rates of systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections.
- Immediate--presumably allergic--reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have had hives or swelling of the lips or tongue, or who have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs--including those who have had occupational asthma or other allergic responses to egg protein--might also be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician should be considered. Protocols have been published for safely administering influenza vaccine to persons with egg allergies.
- Hypersensitivity reactions to any vaccine component can occur. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, the majority of patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity. When reported, hypersensitivity to thimerosal usually has consisted of local, delayed-type hypersensitivity reactions.

Guillain-Barré Syndrome

- The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Among persons who received the swine influenza vaccine in 1976, the rate of GBS was <10 cases per 1 million persons vaccinated. The risk for influenza vaccine-associated GBS is higher among persons aged $\geq$25 years than persons <25 years. Evidence for a casual relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Investigations to date indicate no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976), and that, if influenza vaccine does pose a risk, it is probably slightly more than one additional case per 1 million persons vaccinated.
- The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history. Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might

increase the risk for recurrence of GBS is unknown; therefore, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccination is prudent. As an alternative, physicians might consider using influenza antiviral chemoprophylaxis for these persons. Although data are limited, for the majority of persons who have a history of GBS and who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify yearly vaccination.

Live, Attenuated Influenza Virus

Children

- Signs and symptoms reported more often among vaccine recipients than placebo recipients included runny nose or nasal congestion (20 to 75%), headache (2 to 46%), fever (0 to 26%), and vomiting (3 to 13%), abdominal pain (2%), and myalgias (0 to 21%). These symptoms were associated more often with the first dose and were self-limited.
- Unpublished data from a study including subjects aged 1 to 17 years indicated an increase in asthma or reactive airways disease in the subset aged 12 to 59 months. Because of this, LAIV is not approved for use among children aged <60 months.

Adults

- Among adults, runny nose or nasal congestion (28 to 78%), headache (16 to 44%), and sore throat (15 to 27%) have been reported more often among vaccine recipients than placebo recipients. In one clinical trial, among a subset of healthy adults aged 18 to 49 years, signs and symptoms reported more frequently among LAIV recipients (n = 2,548) than placebo recipients (n = 1,290) within 7 days after each dose included cough (13.9% versus 10.8%); runny nose (44.5% versus 27.1%); sore throat (27.8% versus 17.1%); chills (8.6% versus 6.0%); and tiredness/weakness (25.7% versus 21.6%).

Safety Among Groups at High Risk from Influenza-Related Morbidity

- Until additional data are acquired, persons at high risk for experiencing complications from influenza infection (e.g., immunocompromised patients; patients with asthma, cystic fibrosis, or chronic obstructive pulmonary disease; or persons aged ≥65 years) should not be vaccinated with LAIV. Protection from influenza among these groups should be accomplished by using inactivated influenza vaccine.

Serious Adverse Events

Serious adverse events among healthy children aged 5 to 17 years or healthy adults aged 18 to 49 years occurred at a rate of <1%. Surveillance should continue for adverse events that might not have been detected in previous studies. Health-care professionals should promptly report all clinically significant

adverse events after LAIV administration to the Vaccine Adverse Event Reporting System (VAERS), as recommended for inactivated influenza vaccine.

Antiviral Agents

October 18, 2004 Interim Recommendations

- Use of adamantine may result in adamantine resistance among circulating influenza viruses.
- Pregnant women should consult their primary provider regarding the use of antiviral medications.

April 2004 Recommendations

Amantadine and Rimantadine

- Both amantadine and rimantadine can cause central nervous system (CNS) and gastrointestinal side effects when administered to young, healthy adults at equivalent dosages of 200 mg/day. However, the incidence of CNS side effects (e.g., nervousness, anxiety, insomnia, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine. In a 6-week study of prophylaxis among healthy adults, approximately 6% of participants taking rimantadine at a dosage of 200 mg/day experienced $\geq$1 CNS symptom, compared with approximately 13% of those taking the same dosage of amantadine and 4% of those taking placebo. A study of older persons also demonstrated fewer CNS side effects associated with rimantadine compared with amantadine. Gastrointestinal side effects (e.g., nausea and anorexia) occur in approximately 1 to 3% of persons taking either drug, compared with 1% of persons receiving the placebo.
- Side effects associated with amantadine and rimantadine are usually mild and cease soon after discontinuing the drug. Side effects can diminish or disappear after the first week, despite continued drug ingestion. However, serious side effects have been observed (e.g., marked behavioral changes, delirium, hallucinations, agitation, and seizures). These more severe side effects have been associated with high plasma drug concentrations and have been observed most often among persons who have renal insufficiency, seizure disorders, or certain psychiatric disorders and among older persons who have been taking amantadine as prophylaxis at a dosage of 200 mg/day. Clinical observations and studies have indicated that lowering the dosage of amantadine among these persons reduces the incidence and severity of such side effects. In acute overdosage of amantadine, CNS, renal, respiratory, and cardiac toxicity, including arrhythmias, have been reported. Because rimantadine has been marketed for a shorter period than amantadine, its safety in certain patient populations (e.g., chronically ill and elderly persons) has been evaluated less frequently. Because amantadine has anticholinergic effects and might cause mydriasis, it should not be used for patients with untreated angle closure glaucoma.

Zanamivir

- In a study of zanamivir treatment of influenza-like illness among persons with asthma or chronic obstructive pulmonary disease where study medication was

administered after using a beta2-agonist, 13% of patients receiving zanamivir and 14% of patients who received placebo (inhaled powdered lactose vehicle) experienced a >20% decline in forced expiratory volume in 1 second (FEV1) after treatment. However, in a study of persons with mild or moderate asthma who did not have influenza-like illness, 1 of 13 patients experienced bronchospasm following administration of zanamivir. In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Certain patients had underlying airways disease (e.g., asthma or chronic obstructive pulmonary disease). Because of the risk for serious adverse events and because the efficacy has not been demonstrated among this population, zanamivir is not recommended for treatment for patients with underlying airway disease. If physicians decide to prescribe zanamivir to patients with underlying chronic respiratory disease after carefully considering potential risks and benefits, the drug should be used with caution under conditions of proper monitoring and supportive care, including the availability of short-acting bronchodilators. Patients with asthma or chronic obstructive pulmonary disease who use zanamivir are advised to (1) have a fast-acting inhaled bronchodilator available when inhaling zanamivir and (2) stop using zanamivir and contact their physician if they develop difficulty breathing. No definitive evidence is available regarding the safety or efficacy of zanamivir for persons with underlying respiratory or cardiac disease or for persons with complications of acute influenza. Allergic reactions, including oropharyngeal or facial edema, have also been reported during postmarketing surveillance.

- In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and those receiving placebo (i.e., inhaled lactose vehicle alone). The most common adverse events reported by both groups were diarrhea; nausea; sinusitis; nasal signs and symptoms; bronchitis; cough; headache; dizziness; and ear, nose, and throat infections. Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined.

Oseltamivir

Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%). Among children treated with oseltamivir, 14.3% had vomiting compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect, whereas a limited number of adults enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms. Similar types and rates of adverse events were found in studies of oseltamivir prophylaxis. Nausea and vomiting might be less severe if oseltamivir is taken with food.

CONTRAINDICATIONS

CONTRAINDICATIONS

October 18, 2004 Interim Recommendations for the Use of Antiviral Medications

- Rimantadine is not approved for treatment of children aged

October 5, 2004 Interim Recommendations for Influenza Vaccination

Persons Who Should Not Receive Influenza Vaccine

Persons in the following groups should not receive influenza vaccine before talking with their doctor:

- persons with a severe allergy (i.e., anaphylactic allergic reaction) to hens' eggs and
- persons who previously had onset of Guillain-Barré syndrome during the 6 weeks after receiving influenza vaccine.

April 2004 Recommendations

Persons Who Should Not Be Vaccinated with Inactivated Influenza Vaccine

Inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine without first consulting a physician (see the National Guideline Clearinghouse Summary field "Benefits/Harms of Implementing the Guideline Recommendations"). Prophylactic use of the antiviral agents is an option for preventing influenza among such persons. However, persons who have a history of anaphylactic hypersensitivity to vaccine components but who are also at high risk for complications from influenza can benefit from vaccine after appropriate allergy evaluation and desensitization. Information regarding vaccine components can be found in package inserts from each manufacturer. Persons with acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate the use of influenza vaccine, particularly among children with mild upper respiratory tract infection or allergic rhinitis.

The following populations should not be vaccinated with live attenuated influenza vaccine (LAIV):

- persons aged <5 years or those aged $\geq$50 years
- persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including such metabolic diseases as diabetes, renal dysfunction, and hemoglobinopathies; or persons with known or suspected immunodeficiency diseases or who are receiving immunosuppressive therapies
- children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza infection)
- persons with a history of Guillain-Barre Syndrome
- pregnant women
- persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs

QUALIFYING STATEMENTS

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October 18, 2004 Interim Recommendations for the Use of Antiviral Medications

- These interim recommendations are provided, in conjunction with previously issued recommendations on use of vaccine, to reduce the impact of influenza on persons at high risk for developing severe complications secondary to infection. The recommendations are not intended to guide the use of these medications in other situations, such as outbreaks of avian influenza. These interim recommendations may be updated as more information on the supply of influenza vaccine and antiviral medications becomes available.

April 2004 Recommendations

- Use of trade names and commercial sources is for identification only and does not imply endorsement by the United States Department of Health and Human Services.
- No clinical studies have been conducted regarding the safety or efficacy of amantadine, rimantadine, zanamivir, or oseltamivir for pregnant women; only two cases of amantadine use for severe influenza illness during the third trimester have been reported. However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at substantially high doses. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus (see manufacturers' package inserts).

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

October 18, 2004 Interim Recommendations for the Use of Antiviral Medications

Requesting Influenza Antiviral Medications from the Strategic National Stockpile (SNS)

Influenza antiviral medications in the SNS can be requested only by State or Territory Health Departments. Institutions (hospitals or long-term care facilities) experiencing an urgent need for such medications should convey their request to the State or Territory Health Department.

1. The State or Territory Health Department should call (770) 488-7100, the CDC 24/7 emergency number, to make a request for antiviral medications. A logistics plan is being drafted and will be available to all state and territorial health departments in the near future.

2. The State or Territory Health Department should indicate that there is an urgent priority use situation (as defined previously) that can be addressed by use of antiviral medications, and should indicate that all reasonable efforts have been made to procure influenza antiviral medications from private distributors.

April 2004 Recommendations

Successful vaccination programs combine publicity and education for health-care workers and other potential vaccine recipients, a plan for identifying persons at high risk, use of reminder/recall systems, and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine, including use of standing orders programs. Using standing orders programs is recommended for long-term care facilities (e.g., nursing homes and skilled nursing facilities), hospitals, and home health agencies to ensure the administration of recommended vaccinations for adults. Standing orders programs for both influenza and pneumococcal vaccination should be conducted under the supervision of a licensed practitioner according to a physician-approved facility or agency policy by health-care personnel trained to screen patients for contraindications to vaccination, to administer vaccine, and to monitor for adverse events. A rule from the Centers for Medicare and Medicaid Services (CMS) recently removed the physician signature requirement for the administration of influenza and pneumococcal vaccines to Medicare and Medicaid patients in hospitals, long-term care facilities, and home health agencies. To the extent allowed by local and state law, these facilities and agencies may implement standing orders for influenza and pneumococcal vaccination of Medicare- and Medicaid-eligible patients. Other settings (e.g., outpatient facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, and adult workplaces) are encouraged to introduce standing orders programs as well. Persons for whom influenza vaccine is recommended can be identified and vaccinated in the settings described in the following sections.

Outpatient Facilities Providing Ongoing Care

Staff in facilities providing ongoing medical care (e.g., physicians' offices, public health clinics, employee health clinics, hemodialysis centers, hospital specialty-care clinics, and outpatient rehabilitation programs) should identify and label the medical records of patients who should receive vaccination. Vaccine should be offered during visits beginning in September and throughout the influenza season. The offer of vaccination and its receipt or refusal should be documented in the medical record. Patients for whom vaccination is recommended who do not have regularly scheduled visits during the fall should be reminded by mail, telephone, or other means of the need for vaccination.

Outpatient Facilities Providing Episodic or Acute Care

Beginning in September, acute health-care facilities (e.g., emergency rooms and walk-in clinics) should offer vaccinations to persons for whom vaccination is recommended or provide written information regarding why, where, and how to obtain the vaccine. This written information should be available in languages appropriate for the populations served by the facility.

Nursing Homes and Other Residential Long-Term Care Facilities

During October and November each year, vaccination should be routinely provided to all residents of chronic-care facilities with the concurrence of attending physicians. Consent for vaccination should be obtained from the resident or a family member at the time of admission to the facility or anytime afterwards. All residents should be vaccinated at one time, preceding the influenza season. Residents admitted through March after completion of the facility's vaccination program should be vaccinated at the time of admission.

Acute-Care Hospitals

Persons of all ages (including children) with high-risk conditions and persons aged $\geq$50 years who are hospitalized at any time from September through March should be offered and strongly encouraged to receive influenza vaccine before they are discharged.

Visiting Nurses and Others Providing Home Care to Persons at High Risk

Beginning in September, nursing-care plans should identify patients for whom vaccination is recommended, and vaccine should be administered in the home, if necessary. Caregivers and other persons in the household (including children) should be referred for vaccination.

Other Facilities Providing Services to Persons Aged $\geq$50 Years

Beginning in October, such facilities as assisted-living facilities, retirement communities, and recreation centers should offer unvaccinated residents and attendees vaccination on site before the influenza season. Staff education should emphasize the need for influenza vaccine.

Health-Care Personnel

Beginning in October each year, health-care facilities should offer influenza vaccinations to all personnel, including night and weekend staff. Particular emphasis should be placed on providing vaccinations for persons who care for members of groups at high risk. Efforts should be made to educate health-care workers regarding the benefits of vaccination and the potential health consequences of influenza illness for themselves and their patients. All health-care personnel should be provided convenient access to influenza vaccine at the work site, free of charge, as part of employee health programs.

Influenza Vaccine Supply

During the 2002–03 season, approximately 95 million doses of influenza vaccine were produced, but 12 million doses went unused and had to be destroyed. During the 2003–04 season, approximately 87 million doses of vaccine were produced. During that season, shortages of vaccine were noted in multiple regions of the United States after an unprecedented demand for vaccine lasted longer into the season than usual, caused in part by increased media attention to influenza.

On the basis of early projections, manufacturers anticipate production of 90 to 100 million doses of vaccine for the 2004–05 season.

Influenza vaccine delivery delays or vaccine shortages remain possible in part because of the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains. Steps being taken to address possible future delays or vaccine shortages include identification and implementation of ways to expand the influenza vaccine supply and improvement of targeted delivery of vaccine to groups at high risk when delays or shortages are expected.

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BIBLIOGRAPHIC SOURCE(S)

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Advisory Committee on Immunization Practices (ACIP)

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The preparers of the guideline report have signed a conflict of interest disclosure that verifies no conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

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This guideline is updated annually for each upcoming influenza season.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

May 2004 Recommendations

- HTML Format
- Portable Document Format (PDF)

October 2004 Interim Recommendations

- HTML Format
- Portable Document Format (PDF)

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Guidelines and recommendations. Interim guidance for prevention and control of influenza in the peri- and postpartum settings. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2003 Dec 26. 2 p. Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site.
- 2004-05 flu vaccine shortage: Who should get vaccinated. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2004 Oct 25. 2 p. Electronic copies: Available from the CDC Web site.
- Patient screening form: Who should and who should not get a flu shot? Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2004 Oct 22. 1 p. Electronic copies: Available in Portable Document Format (PDF) from the CDC Web site.

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

PATIENT RESOURCES

None available

NGC STATUS

The original summary was completed by ECRI on July 17, 2000, and updated on October 20, 2000. The original summary was verified by the guideline developer as of January 18, 2001. The summary was updated by ECRI on August 6, 2001, June 12, 2002, May 14, 2003, December 18, 2003, June 15, 2004, and most recently on October 6 and October 30, 2004 in response to interim recommendations published by the CDC on October 5 and October 18, 2004.

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